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* Inventors: The applicant has cited Dr. Friedrich Stolz and Dr. Karl Böttcher from Höchst, in Frankfurt on the Main as inventors.

Patented in the German Empire from February 27, 1927

Title in German of the object of the invention:

Verfahren zur Darstellung von Imidazolderivaten**METHOD FOR THE SYNTHESIS OF IMIDAZOLE DERIVATIVES**

It was discovered that as a result of the action of imidazole or its derivatives upon acetophenons, halogenated in the side chain, or their substitution products, imidazolyl acetophenons are produced, which can be transformed as a result of reduction in accordance with conventional methods into corresponding secondary alcohols. The compounds thus produced exhibit valuable therapeutic properties, and should *inter alia* find an application as cardiac vascular drugs.

Examples

1. Synthesis of phenacyl imidazole (and phenacyl imidazole-bromophenacylate)

199.3 g of ω -bromoacetophenon are dissolved over the course of mild warming in about the doubled amount of alcohol, and to this, there is added - over the course of cooling with ice - a solution of 136 g of imidazole in about the doubled amount of alcohol. Colorless crystals are separated. In order for the reaction to be completed, heating is carried out still for some time on a vapor bath. After the solidification, suctioning, and washing off with acetone and ester takes place out of (filtrate A). The crystals can be purified by means of recrystallization from water, and are melted then at about 250° to 253° over the course of decomposition. The compound thus produced represents the phenacyl imidazole bromophenacylate, having the empirical formula



molecular weight = 385, B calculated 7.27%, found - 7.00%.

The filtrate A is concentrated by evaporation (best of all in vacuum), and the residue is diluted with water. The raw product thus produced can be recrystallized from water or from benzene, and melts then at 117° to 118° . The formula



with a molecular weight 186, befits the raw product, for which formula there was calculated 15.1% N, while 15.04% were found. In alcoholic solution, with the help of alcoholic hydrochloric acid, the compound furnishes a crystalline hydrogen chloride.

2. Synthesis of imidazolyl-propionophenon hydrochloride

To 213 g of α -bromopropionophenon, dissolved in about a triple amount of alcohol, there are added 136 g of imidazole, dissolved in the same amount of alcohol, and heating on a steam

bath is done for some time over the course of reflux condensation. After that, the alcohol is evaporated, and the residue is diluted with water. The oil thus separated or precipitated is absorbed with the help of chloroform, the chloroform solution is dried up with potassium carbonate, and distilled off. The oil residue is dissolved in acetone, and the crystalline hydrochloric salt is precipitated by addition of alcoholic hydrochloric acid. The salt can be purified as a result of recrystallization, and has - in that case- a melting point of 178°, and a composition as follows: $C_6H_5CO CH (C_3H_3) \cdot C_3H_3N_2 \cdot HCl + H_2O$, for which it was calculated: 14.0% H Cl, found 14.09%, and 11.0% N, found 11.24%.

3. Synthesis of imidazolyl acetopyrocatechol and of imidazolylene diacetopyrocatechol

To a solution of 136 g of imidazole in about the same amount of alcohol, there is a solution of 186.2 g of ω -chloroacetopyrocatechol in about the quadruple amount of alcohol, and heating is carried out for a short time above a steam bath, or it is left for longer time at room temperature. After this, flash-off [vaporization] is carried out, the residue is diluted with water, suctioned off, the precipitated is dissolved in diluted hydrochloric acid, and with the help of sodium acetate the solution, which has been clarified with animal charcoal, is precipitated. The suctioned precipitate (filtrate A) furnishes with the help of diluted hydrochloric acid a hydrochloric salt, which is poorly soluble, which can be purified by recrystallization form absolutely diluted hydrochloric acid. The hydrochloric salt thus produced has the formula



having a molecular weight = 404.5, for which 56.36% of C, 4.45% of H, 6.91% N and 8.77% of Cl were calculated, while 56.22% of C, 4.60% of H, 6.97% of N a, and 8.48% of Cl were found.

With the help of iron chloride, its solution in a large amount of water provides a dark-green coloring. The compound is easily soluble in excess amount of alkali,

Filtrate A is precipitated with ammonia, the precipitate is suctioned off, and purified by means of repeated dissolution in diluted acid, and precipitation with the help of ammonia. After the drying, the precipitate constitutes a microcrystalline yellow powder, having the following composition: $C_6H_3(OH)_2 CH_2 CO \cdot C_3H_2 N_2$, mol. weight 218, for which C = 60.5%, 4.6% of H and 12.8% of N were calculated, while 60.2% of C, 4.78% of H and 12.62% of N were found.

4. Synthesis of 4,5-dihydro-2-methylimidazolyl- (= Lysidyl) acetopyrocatechol

To a solution of 164g of 4,5-dihydro-2-methylimidazole (= lysidin) in about the same amount of alcohol, a solution of 186.2 g of ω -chloroacetopyrocatechol in about the quadruple amount of alcohol is added, and heating is carried out of a short period of time on a steam bath, or the mixture is left at room temperature. After that precipitation is done with water, the precipitate is suctioned off, washed off, and treated with diluted hydrochloric acid. After that, a part of the undissolved amount is suctioned off, the filtrate is precipitated with the help of ammonia, and the precipitated residue is purified as a result of repeated dissolution in diluted hydrochloric acid, treatment of the solution with animal charcoal, and precipitation with ammonia. A purely soluble in water microcrystalline yellowish powder, having the composition of: $C_6H_3(OH)_2 CH_2 CO_2 \cdot C_3H_4 N_2(CH_3), 3H_2O$ is thus produced, having a molecular weight of 288, for which 9.72% of N were calculated while 9.58% were found.

5.Reduction of the phenacyl imidazole to α -imidazole ethanol

18.6 g of phenacyl imidazole, dissolved in water, were thoroughly agitated with hydrogen

in the presence of palladous chloride and gum arabic as protective colloid at about 60° and half an atmosphere of excess pressure until 1/10 molecule of hydrogen was absorbed. After that, the free base is rendered Congo-acid, and precipitated with the help of ammonia. As a result of the dissolution in diluted acid and precipitation with ammonia, it can be purified. It has the composition



for which 14.8% of N was calculated while 14.71% was found.

6. Reduction of imidazolyl propionphenon to α -phenyl - β -methyl- β -imidazolethanol

The reduction is carried out in a similar manner as in the preceding examples. The reaction liquid, filtered off from the catalyst, is precipitated with the help of ammonia, and the almost colorless microcrystalline sediment is purified by dissolution in an acid and by precipitation with the help of ammonia. The free base melts at about 170° over the course of the decomposition, and easily dissolved in diluted acids. The aqueous solution furnishes - with the help of iron chloride - an intense green coloring. The free base has the following composition:



having a molecular weight of 220.

8. Reduction of 4,5-dihydro-2-methylimidazolyl-(lysidyl-) acetopyrocatechol to α -,o-dioxyphenyl- β -lysidylethanol

We proceed in exactly the same way as in Example 6, and a hydrochloride is produced, which is very easily soluble in water with a neutral reaction, which hydrochloride is poorly soluble in alcohol, and almost insoluble in ester. Its diluted, aqueous solution is not precipitated by means of alkali. With the help of iron chloride, the diluted aqueous solution brings about an

intense green coloring with the help of iron chloride. The hydrochloride melts at about 198° during decomposition, and has the following composition:



calculated 13.2% of HCl, found 13.22% of HCl.

In a similar way, other imidazole derivatives can be converted with the help other acetophenons, halogenated in the lateral chain, and, self-evidently other reduction means can be used for the reduction of the compounds thus produced.

PATENT CLAIM

Method for the production of imidazole derivatives, characterized in that imidazole or its derivatives are allowed to act upon acetophenons, or their substitution products, halogenated in the lateral chain, and the imidazolyl acetophenons thus produced are converted by means of reduction in accordance with conventional methods into the corresponding secondary alcohols.

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